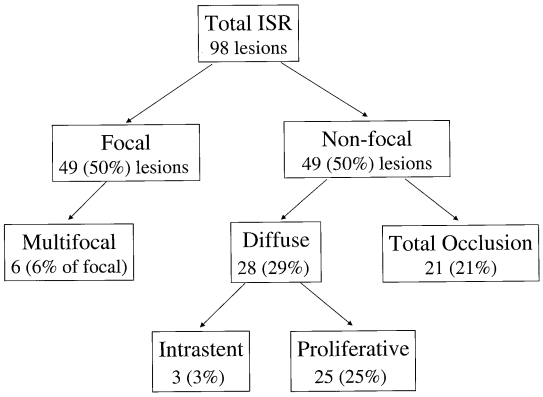

Figure 1. Schematic representation of the patterns of in-stent restenosis (ISR) after paclitaxel-eluting stent implantation.

(29%) (25 diffuse proliferative and 3 diffuse intrastent) and total occlusions in 21 lesions (21%).

Traditionally, the presence of a focal ISR represents a rather benign type of ISR (5). Mehran et al. (4) showed that diffuse intrastent, proliferative, and totally occluded ISR make up a spectrum of increasing disease severity (exaggerated neointimal response). In our study, in contrast to data regarding sirolimus-eluting stents in unselected lesions (6,7), the pattern of ISR after PES implantation was non-focal in 50% of the cases. Whether this finding represents a more exaggerated neointimal response to PES remains to be seen in the ongoing and the upcoming randomized trials between the two types of drug-eluting stents currently available in the market. It is worth noting that in TAXUS IV the pattern of restenosis in 16 lesions with ISR was predominantly focal (62%), but still a considerable percentage (38%) of ISR lesions were non-focal (1). Our study population, compared with TAXUS IV patients, consisted of patients with similar rates of diabetes (26% vs. 24%). However, the mean reference vessel diameter was smaller (2.60 mm vs. 2.75 mm) and the mean lesion length was longer (14.10 mm vs. 13.10 mm). In addition, a greater number of stents per lesion were used in our study (1.23 vs. 1.08). Similar to previous reports with sirolimus-eluting stents, ISR occurred more frequently in the proximal than in the distal stent border (6,7). This finding, which has been attributed to more effective drug effect in the outflow stent border and a possible "wash-out" of the drug, remains to be clarified (7).

The current study presents several limitations. First, this was a retrospective analysis with the inherent caveat of the abscence of a control group. Offsetting this limitation, the data were collected prospectively by independent monitors and entered into a dedicated database, and an independent core laboratory interpreted all angiographic studies. Angiographic follow-up was available in 59% of the patients and in 35% of patients was clinically driven, thereby precluding a homogeneous evaluation of the total restenosis rate for the global treated population. However, the patterns of restenosis were similar between patients that had clinically driven angiography and patients that had systematic elective control angiography. More specifically, out of the 36 ISR lesions in the 28 patients that underwent clinically driven coronary angiogram, 18 (50%) were non-focal; of the 63 lesions in the remaining 53 patients that underwent elective control angiogram, 31 (45%) were non-focal ($p = 0.9$).

In conclusion, restenosis after PES implantation appears in 50% of patients with a non-focal pattern and in the majority of the cases involves the stent edges and more frequently the proximal than the distal border. Diffuse proliferative ISR and ISR with total occlusions are the predominant patterns when non-focal ISR occurs.

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Letters to the Editor

Rescue Angioplasty—The MERLIN Trial

Some of the issues raised by Drs. Grines and O'Neill in their editorial in *JACC* (1) accompanying the Middlesbrough Early Revascularization to Limit Infarction (MERLIN) trial report (2) should be addressed.

Before the trial initiation, we estimated 18% mortality in the conservative group and 6% in the rescue group, as described in the statistical methods section. This may have been optimistic, but was based upon a careful literature search. Power calculations cannot be

made on the basis of data that subsequently become available. In the discussion, we describe a 2% to 12% 30-day or hospital mortality among patients undergoing rescue angioplasty, but it is clear from the reference section that this includes data from studies published after initiation of the MERLIN trial.

It is extraordinary for the authors to suggest that we made the comment that 3,000 patients would be needed to show mortality benefit and that, knowing this, we went on to perform a trial on 300 patients. First, this comment does not actually appear in our study, having been removed (not at our request) during the review and editing process. Second, the figure of 3,000 is an estimation of the number required in each of the two arms in order to demonstrate significant reduction in coronary mortality at *the levels we observed* (11% conservative vs. 8.5% rescue). Their comments imply that the authors have not understood our power calculation and also that they have either reviewed our original study and been subsequently unaware of changes made by the editorial team, or been given the wrong draft to comment on in the editorial process.

We have not stated that the primary end point in the MERLIN trial is negative, but instead that we failed to demonstrate mortality benefit. Presentation of the results in open forum suggests that those in favor of rescue angioplasty have seen a slight benefit in mortality, as well as the perceived advantages of the combined end point, and interpret this as a reason to continue a rescue program. Conversely, skeptics interpret our results as confirming their belief that rescue angioplasty is performed too late to be beneficial.

We agree that the majority (56%) of our patients had nonanterior infarction, but this is not the same as inferior infarction and does not imply anything about infarct size. The investigators state that randomized trials and American Heart Association/American College of Cardiology guidelines suggest that clinical benefit from rescue angioplasty is confined to anterior myocardial infarction (MI). However, this is based almost entirely on data from the RESCUE trial (3), with its limitations as described. No randomized trial has demonstrated lack of benefit from rescue angioplasty in patients with nonanterior MI.

Despite the above comments, we suspect there is no major conflict. A successful rescue angioplasty frequently benefits the patient: the vessel opens, flow is restored, the ST segments come down, and there are no complications. However, it is an omission to make no comment on the potential for harm. The challenge is to identify those patients with most to gain and the lowest risk of harm.

We have not abandoned rescue angioplasty, and certainly not abandoned the open-artery hypothesis. We believe that primary angioplasty is the best treatment for ST-segment elevation myocardial infarction. However, while patients continue to receive fibrinolytics for ST-segment elevation myocardial infarction, the question of rescue remains. Our approach is a selective one, in line with the editorial view. Our current focus is on how to deliver primary angioplasty to a large population in the northeast of England with equitable access to care for all patients. If this can be achieved, the unanswered dilemmas of rescue angioplasty will become relatively less important.

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REPLY

We thank Drs. Sutton and Belder for their interest in our paper (1) and again wish to compliment Sutton et al. (2) on undertaking the largest rescue angioplasty trial conducted to date. It appears that we were using an earlier version of the study when commenting on the required sample size of 3,000 patients, and for this we apologize. But all parties agree that one could not expect a significant reduction in mortality given the small sample size and control group mortality of only 11%.

Although we can debate whether nonanterior myocardial infarction (MI) is the same as inferior MI, it is clear that patients who present with inferior ST-segment elevation have a smaller infarct size (3) and better prognosis than patients with anterior MI (4). Moreover, given the low baseline risk of inferior MI patients, it has been difficult to prove a mortality advantage with reperfusion therapy compared to placebo (4).

So what have we learned from the MERLIN trial? It is clear that rescue angioplasty has room for improvement. Consistently, rates of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 after rescue percutaneous coronary intervention (PCI) are lower than those reported after primary PCI. We had hoped that extraction of thrombosis or use of distal protection devices would improve perfusion and clinical outcomes. Yet large, randomized trials using distal protection (EMERALD trial) or thrombectomy (AIMI trial) showed no improvement in TIMI flow grades, myocardial blush scores, infarct size, or major adverse cardiac events compared to PCI alone (5). The lack of benefit may have been due to embolization with saline agitation, advancing the device past the thrombotic lesion or diverting emboli into proximal side branches. Therefore, it is possible that use of lower-profile thrombectomy catheters, filters, or proximal protection devices may be of benefit.

We agree with the MERLIN investigators that the focus should not be on rescue PCI, but on how to deliver primary angioplasty to a larger population. Performance of primary PCI (by an experienced PCI operator) in a diagnostic-only catheterization laboratory would increase availability enormously. We should work toward a goal of performing prehospital electrocardiography and transferring patients with ST-segment elevation myocardial infarction from home, directly to a primary PCI center.